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Building Interdisciplinarity in Research on Gene Therapy

(Editorial)

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Building Interdisciplinarity in Research on Gene Therapy

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Perceived by many as one of the most promising areas within the emerging practice of molecular medicine, gene therapy combines expertise from genetics, molecular biology, clinical medicine and human genomics. The Human Genome Project broadly defines gene therapy as "a technique for correcting defective genes responsible for disease development".[1] These techniques include primarily the insertion but also the substitution, repair or regulation of genetic material.

Gene therapy relies and draws heavily on our rapidly expanding knowledge of the role of gene–gene and gene–environment interactions in the pathogenesis of many diseases [1,2]. Newly emerging disciplines such as bioinformatics, and innovative technologies such as functional magnetic resonance imaging (FMRI) (see Fairhurst, this volume) are beginning to provide invaluable information on gene expression *in vivo*. This helps to identify inherited or acquired genetic deficiencies and to reveal their (dys)functionality in disease, thereby isolating potential targets for intervention. Linking these knowledges with other findings in molecular biology, biochemistry and material science continually improves our understanding of cellular genomic and metabolic processes. These developments may one day enable the causal treatment of many diseases at the genetic level.

Open any textbook on molecular medicine and gene therapy and you will find a long list of diseases which, the authors promise, will be treated directly or indirectly by means of gene therapy, e. g. cardiovascular diseases, liver diseases, neurological and haematological disorders, cancer, HIV infection and certain forms of arthritis. These are all major diseases that inflict serious pain on patients, often correlate with a range of co-morbidities and in many cases significantly reduce life expectancy or disabilityadjusted life years, respectively, while also presenting a substantial financial burden on national health budgets especially in the industrialised world.

Being able to treat these diseases at their roots, in many ways would introduce a new era in medical practice. Rather than focusing on dealing with downstream symptoms, often using rather unspecific drugs, gene therapy may enable clinicians to operate far upstream

[1] HGP: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml (accessed 18 November 2005).

tackling the genetic defect(s) responsible for the adverse alterations in physiology – in many cases even before they arise. The possibility of upstream interventions will likely foster the development of a form of genetic preventive medicine targeted at the individual or small populations that are sufficiently homogeneous with respect to a particular genetic make-up.

Many members of the research community involved in the development of gene therapy share these visions as far as somatic gene therapy, i. e. the manipulation of genetic material in somatic rather than germline cells, is concerned. Germline interventions intended to produce genetic alterations to be passed on to the next generation present a different topic altogether (Feinberg, this volume). Note that none of the contributors to this volume had any interest in developing germline interventions, nor did they see a need for anyone else to develop that approach to date (Huber, this volume). However, gene therapy *in utero*, i. e. fetal gene therapy "as a third therapeutical option" has been tackled (Meyer, this volume).

Beyond the visions of causal treatment of disease, somatic gene therapy, whether conducted *in* or *ex situ*, faces two major challenges that are being addressed in most current research efforts: gene transfer and appropriate gene expression. Gene transfer ("transfection"), i. e. the delivery of genetic material to the relevant cells, currently relies primarily on the so-called vectors ("gene taxis") and as such is pursued along two different routes: the delivery via the so-called (1) viral vectors (see Burger, this volume, for a review on recombinant adeno-associated viral vectors and O'Donnell and Lewandowski, this volume, on adenoviral gene transfer in the heart) and (2) non-viral or artificial vectors (see Lutz and Cartiers, this volume). All vectors carry their own advantages and disadvantages related to safety and toxicity, DNA carrying capacity, transfection efficiency, availability and costs. Therapeutic gene expression becomes relevant once genetic material has been successfully inserted into the patient's genome and refers to the "frequency of use" of this material. The difficulty lies in achieving a level of expression that leads to an amount of gene product in the body sufficient to abolish the dysfunction without causing significant adverse side effects.

The considerable lack of knowledge about transport, transfection and expression of genes as well as issues related to their long-term functioning means that gene therapy today still carries major risks. Viral material from vectors "going astray" in the body, non-target cells being transfected and significant over- or under-expression of genetic material as well as immunological challenges in the course of the transfection process are difficult to control, yet carry the potential to seriously disrupt physiological processes. The issue of unknowable unknowns aside [3], even a comprehensive and reliable risk assessment remains difficult due to the incomplete understanding of the complexities of gene expression *in vivo*.

In the context of these significant uncertainties, two early applications of gene therapy have caught the public's and the media's attention in Europe as well as the in US. In 1999, a 19-year-old student died during a gene therapy trial in the US due to multiple-organ collapse caused by an immune response against the adenoviral vector because of poorly

conceived protocols and malpractice (Feinberg, this volume).[2] In 1999 and 2002 in France (Hôpital Necker, Paris), the gene therapeutic treatment of 11 patients with severe chronic immunodeficiency X1 (SCID-X1) led to their cure but caused leukaemia in three of them (Feinberg, this volume).[3] To the public, these trials demonstrated, first and foremost, gene therapy's serious potential for adverse outcomes. To much of the scientific community, they showed that gene therapy worked in principle, yet at the same time brought home the current lack of comprehensive knowledge. The resulting media coverage and public anxiety and mistrust led to a significant decrease in the enthusiasm related to the development of gene therapy. Despite intensive discussions about possibilities to interrupt a clinical research protocol for clinical, scientific and/or ethical reasons (Sergent, this volume) and more generally about ways of assessing risks associated with gene therapy and re-building critical public trust (Thalmann and Fairhurst, this volume), much of public and private funding for basic research dried up, significantly slowing progress in this area. Promises of gene therapy have persisted and an increasing number of products has entered clinical trials. In China, the first drug based on gene therapy, "Gendicide", has apparently been brought to the market recently (Döring, this volume). Nevertheless, most members of the relevant research communities concede that "... current gene therapy is experimental and has not proven very successful in clinical trials. Little progress has been made since the first gene therapy clinical trial ...".[4]

The role of public perception and trust in technology and risk assessment is being emphasised in Europe as well as in the US for some time now [4–7]. Many procedures have been developed to better understand the potential developments of a particular technology and assess its benefits and risks while taking into account public concern. Scenario workshops, Delphi studies and other forms of participatory technology assessment have been described in detail elsewhere (e. g. Ref. [8]) and currently operate in Europe as well as in the US with some success (Schmidt, this volume). Therapy and drug development has so far invoked little public controversy as it has been seen as yielding high benefits while operating within a tightly controlled regulatory regime. While this used to hold for much of medical technology and practice, recent scandals in Europe over blood transfusion, vaccines or organ donation have begun to taint the medical profession's image [9]. Gene therapy, as a practice on the borderline between research and medical practice, presents a somewhat different and more complex case raising a host of ethical issues, from screening and informed consent to negative eugenics or even enhancement (Ganguli and Feinberg, this volume) as well as questions related to public perceptions of risk and trust in regulatory regimes (Schmidt, this volume).

Many members of the natural science as well as the technology assessment community subscribe to the view that these issues should be resolved via ethical reflection and improvement of the public's understanding of science and technology [10]. Some would go further to include members of the public in technology assessment panels in an attempt

[2] See also geoscience-online from http://www.g-o.de (accessed 16 November 2005).

[3] Also press release Paul Ehrlich Institute from 28 January 2005: http://www.pei.de

[4] HGP: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml (accessed 18 November 2005).

to broaden the knowledge base with which developments are assessed [11,12]. While these approaches are perceived by most as useful, they implicitly perpetuate the view that scientific practice is able to control and evaluate itself while its outputs need to be debated in a broader context. A subtle critique of this perception of science as removed from and untainted by social practice argues for transparency of scientific process and an emancipation of different kinds of knowledges (e. g. Refs. [13–15]).

This volume is based on an interdisciplinary workshop, which tried to take this critique seriously. Rather than understanding science and medicine as monolithic bodies of knowledge and practice, the workshop was based on an understanding of gene therapy as an epistemic culture [16], i. e. a web of different practices that contribute to the production of a contingent body of knowledge. Accepting this historical and social contingency of present knowledge and practice [17] shifts the emphasis from a reflection of scientific output by experts external to the particular area of science under consideration, to a focus on scientific practice, which necessarily involves the practitioners themselves. The aim is a change in culture, which introduces into scientific practice a process of reflection enabling the practitioners to appreciate the contingency of their own gaze. It is important to note that science in this case does not only refer to the natural sciences and medicine but includes the social sciences and humanities. The process of understanding the contingency of the own gaze via learning to think differently applies to all those involved in highly specialised disciplines.

This concept in mind, the workshop brought together young post-docs from a wide range of different disciplines for a week explaining and debating their own work as well as interviewing more established researchers in the field. Of course, this can only be a small step. Yet the sessions illustrated that trying to understand each other's work in practice, i. e. excitement, daily routines, constraints, visions and anxieties, can help to de- and re-contextualise one's own work. A *trans*disciplinary group process, that transfers knowledges from one discipline to another, begins to produce *inter*disciplinary individuals able to ask research questions located *in between* disciplines. The book chapters are based on the initial contributions of all participants and reflect an intensive process of internal review and rewriting on the basis of the discussions. They are meant to present the outcome of an interdisciplinary experiment rather than reflecting the entire field of gene therapy. Many issues could not be dealt with. Readers interested in comprehensive reviews of gene therapy are pointed to recent articles [18,19] as well as specific journals in the field.

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This book is the outcome of a European interdisciplinary workshop of young post-doc scientists from the natural and social sciences as well as the humanities, which took place at the Max-Delbrueck-Center for Molecular Medicine (MDC), Berlin Buch, in May 2005. We thank all participants for working extremely hard to put this volume together. Particular thanks goes to Ali ben Salem, whose hard work during and around the workshop has been absolutely essential for realizing this project. The individual chapters

represent the participants' written contributions, which were substantially revised on the basis of the discussions. The statement on forthcoming challenges in research and policy was supported by all participants as a consensus paper. Four authors from the US and Pakistan were invited to broaden the European perspective of this book (Mehmood et al.; Burger; Feinberg; O'Donnell and Lewandowski, this volume). The workshop was funded by the German Ministry of Education and Research, grant no. BMBF 01 GP 0482.

Appendix: Consensus Paper

We still have a poor understanding of the underlying mechanisms of gene transfer. Public funding is necessary to support the fundamentals of gene therapy.

Gene therapy is now understood as an interdisciplinary research field. Tools have to be developed or adapted from other research areas with an interdisciplinary approach in order to render gene therapy research more efficient (e. g. standardisation, harmonisation, communication).

There is a gap between the availability of molecular diagnostics and that of molecular therapeutics for a variety of diseases.

Consideration should be given to setting limitations to restrict genetic intervention to therapeutic application.

Communication needs to be established and facilitated not only between experts and public but also between the experts themselves, both within the same and between different fields.

Communication of issues related to gene therapy has to respect a balance between transparency and privacy of information, clarity and consistency.

One of the characteristics of gene therapy is that its clinical effects are not fully predictable. It contains various forms of uncertainty and these must be acknowledged and communicated.

Terminology and vocabulary describing gene therapy must be carefully created and used. The concept behind the terminology is of primary importance and should be considered when crossing cultural or national borders. For example, even the term "gene therapy" may create false expectations or fears.

Information should not only include technical aspects about gene therapy but also all processes pertaining to its application (e. g. regulation, conditions, legislation).

Two-way communication is essential as well as constant appreciation of public awareness. The channels through which this bidirectional information is distributed have to be carefully created and constantly refined.

Information should be put forward in an accessible manner, specific to the target audience.

Taking these points into consideration may allow for a better grounding for a truly informed decision base.

Taboos should be questioned in the public debate and legislation process.

There is a need to set a flexible framework to regulate gene therapy in order to adapt to the rapidly changing scientific knowledge and social perception. It is possible to establish

an independent regulatory body, which would be able to work on a case-by-case basis. It is very important that this body is not only made up of an expert panel but allows for public hearing and public participation.

The legislative process for gene therapy can be made more flexible and expedient. For example, ensure that laws are revised at regular intervals.

It is important to reach a consensus about terms as well as concepts at the European level while allowing for applications and enforcement to be regulated within the national context.

Review the grounding behind legislation. Do our laws protect what we want them to? What is our concept of life, privacy, risk, appropriate use, individual freedom, and future generation choice? One of the key distinctions is that between therapy and enhancement. Public discussion should be encouraged in order to contribute to the definition of concepts (e. g. through surveys and online consultations).

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